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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/473,551	12/28/99	MILBRANDT J	6029-9879

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EXAMINER	
CHERNYSHEV,O	
ART UNIT	PAPER NUMBER
1646	13

DATE MAILED: 09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/473,551	MILBRANDT ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 28 December 1999 is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. The claims 10-36 have been cancelled as requested in the amendment of Paper #11, filed on August 02, 2001. Claims 1-9 are pending in the instant application.

Applicant's election without traverse of Group I in Paper No. 11 is acknowledged.

Applicants' arguments regarding election of a single growth factor embodiment were considered but not found persuasive. Applicants argue that human, mouse and rat persephin (SEQ ID NO:1-3) are a number of species within the genus of persephin. The Examiner disagrees with the argument because in the instant case the different forms of persephin (human, mouse and rat) are representing chemically, structurally and functionally different compounds, which can be made and used without each other, therefore representing patentably distinct inventions itself. It is therefore concluded that claimed different persephin molecular embodiments containing specific amino acid substitutions constitute independent and patentably distinct inventions, since they all have different chemical structures, different functions, and can be made and used without each other (see MPEP § 806.04, MPEP § 808.01).

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-9 are under examination in the instant office action.

Drawings

2. The drawings filed on 12.28.99 are acceptable subject to correction of the informalities indicated on the attached "Notice of Draftperson's Patent Drawing Review," PTO-948. In order to avoid abandonment of this application, correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim1-3 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for growth factors identified as PGP-F2ac, PNP-F2ac and PAP-F2ac, does not reasonably provide enablement for growth factors of claims 1-3 and 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-2 and 9 are directed to a growth factor for which no structure is provided, which has a function to activate GFRα1-RET but does not substantially activate GFRα2-RET or GFRα3-RET. However, the instant specification provides neither guidance, nor adequate description for any and/or every growth factor that can possess such a function, including all the possible variations of chimeric GDNF family ligands or derivatives thereof. The instant specification only teaches certain examples of such growth factors, namely PGP-F2ac, PNP-F2ac and PAP-F2ac (see Examples of the instant specification and also Figure 6).

Similarly, claim 3 is directed to a chimeric growth factor with no explanation or guidance as to what the substitutions should be present to achieve the structure, which will provide the desirable function, such as to activate GFRα1-RET but does not substantially activate GFRα2-RET or GFRα3-RET. Again the only chimeric proteins adequately described in the instant

specification are PGP-F2ac, PNP-F2ac and PAP-F2ac. Therefore, considering the breadth of claims 1-3 and 9, lack of guidance and unpredictability of the results (see Examples of the instant specification, indicating that even slight deviation in molecular structure of tested chimeric constructs leads to different degree of ligand binding to a specific receptor), it would require undue experimentation for a skilled artisan to practice the claimed invention.

4. Claims 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6-8 are directed to the human persephin of SEQ ID NO:1 with substitutions for amino acid residues of SEQ ID NO:17 and SEQ ID NO:20, which comprises SEQ ID NO:23 or consists of SEQ ID NO:26. However, the instant specification does not provide enough guidance, except from disclosure of amino acid sequences of preferred molecular embodiments, that these particular chimeric proteins might act as growth factors, which activate GFRα-1 RET but does not substantially activate GFRα-2 RET or GFRα-3 RET. Therefore, it would require undue experimentation of one skilled in the art to discover how to practice the present invention as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

It is known from the literature and also stated in the instant application that "the placement of GDNF, neurturin, persephin, and artemin into the same growth factor family [] is based on the similarities of their physical structures and biological activities. For example, human persephin has about 40% sequence identity and about 43% sequence conservation with human GDNF; about 49% sequence identity and 50% sequence conservation with human neurturin; and about 45% sequence identity and 48% sequence conservation with human artemin" (page 2, lines 28-34 of the instant specification). However, it is also known in the art that these particular growth factors, GDNF, persephin, neurturin and artemin represent ligands for different types of receptors, namely GFRα-1, 2, 3 and 4 RET. It is logical to assume that in this particular case, as well as in case of other growth factors, different, even slight variation in structure can lead to unpredictable results in terms of biological activity of a particular factor. Since the instant claims are directed not to chimeric proteins but to growth factors having particular molecular structure, it is important to know if the claimed proteins can be identified as growth factors. Without a precise protocol, confirmed with statistically analyzed data about biological activity of claimed proteins, it is impossible to conclude that claimed chimeric proteins can indeed possess a function, which will substantiate their belonging to the family of growth factors. However, the instant specification fails to provide the functional support for the claimed proteins. The examples presented in the specification are directed to rat and mouse chimeric persephin. Extrapolation of the results presented in the examples would only lead to assumption that human persephin chimeric protein would have similar biological activity, which has to be proven by undue experimentation in order for a skilled artisan to practice the claimed invention.

In view of the lack of teachings and unpredictability of the art set forth earlier, and also the total absence of the working examples, the instant specification is not found to be enabling for growth factors of claims 1-9. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 2 is indefinite because it is not clear from the structure of the claims derivative of what molecular embodiment is encompassed by the claim. It seems that it can be either derivative of growth factor of claim 1 or of a chimeric GDNG family ligand. Clarification is required.

7. Claim 3 is indefinite because the phrase "or conservative amino acid substitutions therefore" does not adequately explains what region is substituted, e.g. regions of F2a or regions of GDNF, neurturin or artemin. Clarification is required.

8. Claims 4 and 5 are indefinite because the substitutions of claimed SEQ ID numbers are not among those elected by the Applicants. Therefore, it is impossible to specifically identify what growth factors are claimed.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Jing et al. (J. Biol.Chem, 272, No.52, pp.33111-33117, 1997; reference AR) as evidenced by Worby et al. (J.Biol.Chem., 273, No.6, pp.3502-3508, 1998; reference BG).

Jing et al. (1997) teach a growth factor, GDNF which activates GFRα1-RET but does not substantially activate GFRα2-RET (see Fig 5 on page 33115 and second column, lines 11-12 especially). It appears that neurturin actives GFRα2-RET with ability of binding about 100-1000-fold higher than GDNF itself, which falls into the category of "substantially activate".

Worby et al. (1998) teach that GDNF does not bind to GFRα3-RET (see page 3504, second column, page 3505, first paragraph and Fig.3B). Therefore, according to Worby et al. (1998), GDNF is a growth factor, which activates GFRα1-RET but does not substantially activate GFRα3-RET.

10. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al. (WO009733911).

Johnson et al. (WO009733911) teach chimeric protein, PSP/NTN of mouse persephin, a growth factor belonging to a chimeric GDNF family ligand.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jing et al.

The disclosure of Jing et al. is provided above. Jing et al. do not teach pharmaceutical composition. However, it would be obvious to a person of ordinary skill in the art at the time the invention was made to use the claimed growth factor of Jing et al. in combination with a pharmaceutically acceptable preparation for therapeutic use. One of ordinary skill in the art would be motivated to do so because Jing et al. teach GDNF is a neurotrophic factor for cells of the CNS and the administration of such for this purpose would require the presence of a pharmaceutically acceptable preparation.

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications and (703) 308-0294 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.
September 8, 2001 OC

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud